PATENT CASE
OC01121K

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF APPEALS AND INTERFERENCES

In re Application of:	
Sara L. Zaknoen	Examiner: Sheela Jitendra Huff
For Patent For: **Combination Therapy for Cancer**	Group Art Unit: 1642
Serial No.: **09/767,424**	Date: January 14, 2004
Filed: **January 22, 2001**	

Schering-Plough Corporation
Kenilworth, New Jersey 07033-0530

Mailstop: Appeal – Briefs
P.O. Box 1450
Commissioner for Patents
Alexandria, VA 22313-1450

REPLY BRIEF TO EXAMINER'S ANSWER

Sir:

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO COMMISSIONER FOR PATENTS, ALEXANDRIA, VA 22313-1450 ON

1/14/2004
(DATE OF DEPOSIT)

WILLIAM Y. LEE, REG. NO. 46,100
(REGISTERED REPRESENTATIVE)

William Lee 1/14/2004
(SIGNATURE AND DATE)

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I. REAL PARTY OF INTEREST

Schering Corporation, Galloping Hill Road, Kenilworth, New Jersey 07033, is the real party of interest for the above identified application.

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals, and there are no interferences, for the above identified application which will directly affect or have a bearing on the Board's decision in this Appeal.

III. STATUS OF CLAIMS

A. Pending Claims:

Claims 1-22 are pending. (See Appeal Brief filed September 23, 2003 for listing of claims). No claims have been amended with the filing of this paper.

B. Appealed Claims

Claims 1-22 are being appealed.

IV. STATUS OF AMENDMENTS

No amendments have been made to the claims throughout the prosecution. A response to a rejection under 35 U.S.C. 103, was filed after the final rejection of April 23, 2003. In an Advisory Action dated July 25, 2003, the Examiner stated that the July 23, 2003 Response to the Office Action (Continuation of 5), does not place the application in condition for allowance because it reiterates appellant's previous arguments which were addressed in previous Office Actions. On September 23, 2003, appellant filed an Appeal Brief. The Examiner sent an Examiner's Answer

dated November 18, 2003, to which appellant is presently filing this paper in response. No amendments have been made since appellant's filing of the September 23, 2003 Appeal Brief.

V. SUMMARY OF THE INVENTION

This invention is directed to a method for treating a human patient afflicted with cancer, comprising administering therapeutically effective amounts of temozolomide and pegylated interferon alpha to such a patient. The temozolomide is administered to the patient in combination with the pegylated alpha interferon; that is, the temozolomide and pegylated interferon alpha doses are administered during the same treatment cycle.

VI. ISSUE

Are claims 1-22 unpatentable under 35 U.S.C. 103(a) over the WO 97/12630 in view of Ragab, U.S. 6,346,524 and Kline U.S. 6,180,096 or WO 95/13090?

VII. GROUPING OF CLAIMS

The rejected claims stand or fall together.

VIII. THE ARGUMENT

The cited references do not teach, disclose or suggest Appellants' claimed invention.

Appellants' claimed invention is directed to a method for treating a human patient afflicted with cancer, comprising administering therapeutically effective amounts of temozolomide and pegylated interferon alpha to such a patient.

The combination of cited references does not suggest that temozolomide and pegylated interferon alpha can be used to treat cancer.

As previously stated, the Examiner has rejected claims 1-22 under 35 U.S.C. 103(a) as being unpatentable over the WO 97/12630 in view of Ragab, U.S. 6,346,524 and Kline U.S. 6,180,096 or WO 95/13090.

In the Examiner's Answer to the appellant's Appeal Brief, the Examiner reiterated her position regarding the obviousness rejection of claims 1-22.

Because of the differences between the scope of the prior art and the claimed invention, per the Graham factors, Appellant respectfully maintains all of its previous arguments that a prima facie case of obviousness cannot be established. Furthermore, with the filing of this paper, Appellant wishes to particularly address the Examiner's position that "it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to use interferon alpha 2b linked to PEG 12000 to form a more stable, long-acting interferon alpha 2b." (See page 4, lines 6-7 of Examiner's Answer)

Appellant claims a method of treatment using therapeutically effective amounts of temozolomide in combination with **pegylated** interferon alpha. (See page 3, lines 16-27 and pages 6-7, lines 25, et al. of appellant's specification) **Pegylated** interferon alpha is described on page 4, lines 12-20 of the specification, as the polyethylene glycol modified conjugates of interferon alpha.

WO 97/12630 discloses the combination therapy of temozolomide and, interferon alpha, specifically interferon alpha 2b (see generally, Abstract, pages 4-5 of the specification and claims 1-21). Absent the teaching of pegylated interferon in WO 97/12630, the Examiner relies upon the references Kline and WO 95/13090 for their disclosure of PEG interferon alpha 2b (see generally, Abstract, for both references).

Finally, the Examiner cites Ragab and its use of temozolomide **alone**, (see generally, Abstract, col. 2, lines 31-45 and claims 1-11 of Ragab).

As appellant has maintained throughout the prosecution of this application, contrary to the Examiner's assertion, the use of pegylated interferon and temozolomide for treating cancer is not obvious in view of the references cited by the Examiner for the following reasons.

The molecular and pharmacokinetic properties of pegylated interferon alpha and non-pegylated interferon alpha are different from one another such that the two molecules should be considered to be different drugs. Pegylation changes the chemical nature of the molecule from a protein to a protein-polymer conjugate. Further, pegylation increases the molecular weight of the interferon alpha molecule; PEG-INTRON, a pegylated interferon alpha 2b, has molecular weight of 31 kDal, compared to a molecular weight of approximately 19 kDal for non-pegylated interferon alpha 2b. Pegylation of interferon alpha also increases the plasma half-life compared to that of the unconjugated interferon alpha.

The increased half-life of pegylated interferon alpha relative to that of the non-pegylated form significantly changes certain pharmacokinetic properties of the pegylated molecule. One pharmacokinetic property that can be important in treating certain diseases is the total dose exposure, also referred to as the area under the concentration-time curve or AUC, a measurement of the patient's total exposure to a drug over a period of time. Another important pharmacokinetic property is the peak plasma level of a drug, also referred to as C_{max}, which is a measurement of the maximum drug concentration achieved in the patient after administration of the drug.

Due to the longer half-life of pegylated interferon alpha compared to that of the non-pegylated form, the relationship of peak plasma levels to total drug exposure is different for pegylated interferon alpha compared to that of non-pegylated interferon alpha. Administration of pegylated interferon alpha to achieve a similar total drug exposure of interferon alpha activity as treatment with non-pegylated interferon alpha results in peak plasma levels of interferon alpha that are lower than treatment with non-pegylated interferon alpha. Conversely, administration of pegylated interferon alpha to achieve a similar peak plasma level of interferon alpha activity as that of non-pegylated interferon alpha results in total drug exposure much higher than those achieved using non-pegylated interferon alpha.

It is known to one having ordinary skill in the art that a particular pharmacokinetic parameter of a drug is often essential for treating a particular disease. In some cases, a patient's total exposure to the drug is critical for treatment. In other cases, the peak plasma level of a drug is important for successfully treating a disease. The peak plasma level of a particular drug may be essential for treating one disease while the total drug exposure of the same drug may be important for treating a different disease. It is also known to those having ordinary skill in the art that the total drug exposure of one drug may be more important for effectively treating a particular disease, while the peak plasma level of a different drug maybe critical for treating that disease.

The efficacy of a drug with respect to a particular disease cannot be predicted based upon treatment of that disease with a structurally and functionally distinct drug. Thus, one having ordinary skill in the art could not predict for pegylated interferon alpha whether the total drug exposure or its peak plasma level would be important in treating cancer because pegylated interferon alpha and nonpegylated interferon alpha are different drugs. Thus, the references cited by the Examiner are not predictive of treating cancer with pegylated interferon alpha and temozolomide.

Therefore, because of the above statements and those previously made in the prosecution of this case, Appellant respectfully submits that the claimed invention is not obvious in light of Ragab, Kline, WO 97/12630 and WO 95/13090.

Appellant and the Examiner are both in agreement that WO 97/12630 does not teach the use of pegylated interferon. However, Appellant respectfully suggests there is no suggestion or motivation from WO 97/12630, Kline, WO 95/13090 and Ragab to combine their teachings together to render the present invention, a method of treatment using therapeutically effective amounts of temozolomide in combination with pegylated interferon alpha, obvious under § 103. None of the references cited, either singly or in combination with each other, suggest the Appellant's claimed method of combination therapy with temozolomide and pegylated interferon. Furthermore, there is no teaching in any of the cited references that temozolomide and pegylated interferon-α can be synergistically combined. Appellant respectfully suggests that the only suggestion to combine the teachings of the cited references comes from the Appellant's specification itself. "There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from Appellant's disclosure".

Therefore, the Board of Appeals is respectfully requested to reverse the rejection of Claims 1-22 and to allow these claims to issue.

Respectfully submitted,

William Y. Lee
Reg. No. 46,100
Attorney for Appellant
(908) 298-2161